38. (Amended) The method of Claim 1, wherein a gene expression product is isolated from at least ten informative genes from one or more cells in said sample and wherein a gene expression profile of said at least ten informative genes is determined.

39. (Amended) The method of Claim 15, wherein a gene expression product is isolated from at least five informative genes from one or more cells in said sample and wherein a gene expression profile of said at least five informative genes is determined.

40. (Amended) The method of Claim 15, wherein a gene expression product is isolated from at least ten informative genes from one or more cells in said sample and wherein a gene expression profile of said at least ten informative genes is determined.

Amendments to the claims are indicated in the attached "Marked Up Version of Amendments" (pages i-ii).

REMARKS

Rejection of Claims 1-5, 8, 15-20 and 37-40 Under 35 U.S.C. §112, First Paragraph

The Examiner rejects Claims 1-5, 8, 15-20 and 37-40 under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in such a way as to enable one skilled in the art to make and/or use the invention. The Examiner asserts that although the specification, combined with the prior art, are enabling for classification of a lymphoma type by determining expression of a bcl-6 gene rearrangement, the specification and prior art are not enabled for the invention as claimed.

Applicants respectfully traverse this rejection. As discussed below, Applicants have identified 100 informative genes, have clearly identified which genes are upregulated and downregulated with respect to specific class distinctions, have described algorithms for taking gene expression data and using such data to identify classes, and have described methods for assessing the accuracy of the predictions (see, for example, "Exemplification"). One of skill in the art is guided by the specification as to how to identify informative genes (see, for example,

page 8, line 23 through page 9, line 4 and page 14, lines 10-22 of the Specification), how to obtain expression data from informative genes from samples (see, for example, page 9, line 14 through page 11, line 16 of the Specification), and how to compare the expression profile to a reference expression profile such that a determination can be made as to whether the sample correlates to the reference (see, for example, page 9, lines 5-13; page 11, line17 through page 13, line 5; and page 14, lines 3-9 of the Specification).

As such, one of skill in the art is enabled to practice the steps of the claimed invention, namely, isolating a gene expression product from two or more informative genes from one or more cells in said sample; and determining a gene expression profile of two or more informative genes, wherein the gene expression profile is correlated with a treatment outcome, thereby classifying the sample with respect to treatment outcome.

In light of the disclosure of the Specification, the identification of informative genes and determination of gene expression profiles would require at most nothing more than routine experimentation by one of skill in the art using methods described in the Specification and known in the art at the time of filing.

Breadth of the Claims

The Examiner asserts that, as broadly claimed, the phrase "informative gene" encompasses any gene within a cell. The Examiner further asserts that the classifications "treatment outcome", "survival after treatment", and "lymphoma type" are very broad categories into which samples can be classified.

Applicants do not agree with the Examiner's assertion that "informative gene" encompasses any gene within a cell. In the Specification, on page 8, line 11, "informative genes" are described as "[t]he genes that are relevant for classification." The Specification provides methods for identifying which gene or genes are relevant for making a class distinction, based on their ability to inform such distinctions. For example, a gene whose expression is not altered in a sample obtained from a particular class with respect to a sample obtained from a different class would not be an informative gene since its gene expression pattern could not be used to distinguish the two classes. Therefore, only specific genes useful for making class distinctions are encompassed. The Specification, as noted above, describes methods for identifying

informative genes. Indeed, using such disclosed methods, Applicants have identified and disclosed 100 informative genes that are useful in distinguishing various classes. Therefore, although the group of informative genes includes genes in addition to the 100 genes specifically disclosed, it is not unlimited so as to encompass any gene within a cell.

Moreover, the broad scope of the classes to be distinguished in and of itself does not affect the patentability of the claimed invention if, as here, the claim is fully enabled.

Amount of Direction and Guidance

The Examiner asserts that the specification does not provide guidance as to whether the 100 genes described in FIGS. 1, 2A and 2B exhibit increased or decreased expression in connection to the presence of DLCL. Applicants point out that FIG. 1 is a list of "Large B-Cell Lymphoma treatment outcome gene markers: genes whose expression is increased in low risk and decreased in high risk individuals"; FIG. 2A is a list of "Large B-Cell Lymphoma treatment outcome gene markers: genes whose expression is decreased in low risk and increased in high risk individuals"; and FIG. 2B is a continuation of the list staring in FIG. 2A. Therefore, one of skill in the art can clearly determine which genes exhibit increased expression for high-risk individuals and which genes exhibit decreased expression for high risk individuals, and the converse for low risk individuals.

The Examiner further asserts that, with respect to predicting treatment outcome (Claim 1), survival after treatment (Claim 8) and classification as to lymphoma type (Claim 15), the specification does not give any guidance regarding how the changes in the expression levels of informative genes is used to make predictions. In addition to the genes disclosed in FIGS. 1, 2A and 2B, Applicants describe in FIGS. 3A and 3B informative genes whose expression is increased in DLCL and decreased in FL. In FIGS. 4A and 4B, Applicants show informative genes whose expression is decreased in DLCL and increased in FL. This information, when analyzed by, for example, one of the methods described in the Specification for making class distinctions, *e.g.*, a weighted voting algorithm, would clearly allow one of skill in the art to make class distinctions based on differential expression levels of two or more genes (as above, see, for example, page 9, lines 5-13; page 11, line 17 through page 13, line 5; and page 14, lines 3-9 for an overview of comparison methods and for a specific example of how such a comparison was

actually made). Therefore, Applicants not only describe, but also disclose a working example for, classifying lymphoma types.

State of the Prior Art

Applicants agree with the Examiner that the teachings of Golub *et al.* provide no guidance that would allow a skilled practitioner to correlate specific changes in specific genes with the classification or outcome of lymphoma. However, Golub *et al.* describe methods for making class distinctions based on differential gene expression. The teachings of Golub *et al.* demonstrate that particular algorithms described in the specification were known to one of ordinary skill in the art at the time of filing.

Existence of Working Examples

The Examiner asserts that the Specification does not give any guidance regarding how the changes in the expression level of specific informative genes predict patient survival, nor does the specification teach how the accuracy of the predictions is determined. As above, Applicants believe that there is substantial guidance as to which genes are differentially expressed and how they are differentially expressed (either upregulated or downregulated with respect to a particular class), such that comparison of gene expression profiles would indicate particular class distinctions. Also, as discussed above, there is a working example provided in the Specification.

Level of Predictability in the Art

The Examiner points out that single gene expression profiles can exhibit unsatisfactory linkage to a classification. Applicants note that the claims, as amended, recite correlation of gene expression profiles of two or more informative genes. The ability to identify more than one informative gene and to use gene expression profiles of two or more informative genes clearly allows for more accurate predictions. "Typically the accuracy of the classification will increase with the number of informative genes assessed, thus increasing the confidence level of the prediction." (Specification, page 8, lines 18-20)

Quantity of Experimentation Required

The Examiner asserts that in order to practice the claimed invention, one of skill in the art would be required to perform excessive trial and error experimentation in order to determine which genes would be "informative" for a given type of lymphoma.

Applicants respectfully disagree with the Examiner on this point. "The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." MPEP, §2164.06 citing *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Applicants point out that the Examiner's assertions that the experimentation required would possibly take years or with regard to the number of times an experiment would need to be performed in order to achieve statistical significance are irrelevant in light of *In re* Wands. The length of time or overall amount of experimentation is not the test- if the experimentation is 'routine' in light of the specification and typical practice in the art.

The Examiner asserts that one of skill in the art would be required to perform excessive trial and error experimentation to identify informative genes and determine how differential expression of those genes could be used to predict class or treatment outcome. Additionally, the Examiner then describes scientific standards for making scientific conclusions, for example, repetition of experiments at least three times. Applicants point out, as above, that methods for identifying informative genes are disclosed, and indeed, using these methods, 100 informative genes were identified and disclosed. One of skill in the art need only apply the methods as disclosed to identify informative genes. Indeed, MPEP §2164 states, "The fact that experimentation may be complex does not necessarily make it undue." Additionally, Applicants have disclosed methods and incorporated other methods by reference that demonstrate one of skill in the art would know how to use differential gene expression profiles to distinguish the classes as claimed by the invention. Lastly, repetition of experiments cannot be undue in light of *Wands* if the methods are disclosed. Certainly if the Specification and the state of the art at the time of filing provide for reasonable guidance for the first instance of the experiment, they would also provide reasonable guidance for repeat experiments. However time consuming or extensive the experimentation may be, it does not meet the "undue" standard as described in *Wands*.

The Examiner continues with respect to classification and treatment outcome that one of skill in the art would have to objectively classify each sample, and wait (possibly for several years) to determine the clinical outcome for each patient from which the sample was isolated. After objective classification of the samples and determination of clinical outcome, the Examiner states, one of skill in the art could then begin the process of determining which changes in gene expression are correlated with either classification or outcome in a statistically significant manner. (Page 7 of the Office Action). Applicants point out that a lengthy timeframe for experimentation is not necessarily undue if the specification reasonably guides one of skill in the art to practice the claimed invention. Therefore, the fact that such a process might take several years is not dispositive in determining whether undue experimentation is required. Additionally, Applicants do not agree that said experimentation will necessarily span an extended time period. Applicants point out, for example, that the Examiner has not considered the fact that one of skill in the art could obtain a sample from a class already diagnosed by a different method and generate a reference gene expression profile based on the prior diagnosis, eliminating the delays the Examiner considers inherent. Additionally, one of skill in the art would not necessarily have to determine the treatment outcome of a patient, as the Examiner seems to suggest, if a sample were obtained from a patient whose treatment outcome was already known. Such samples could be used to create a reference gene expression profile and future classifications would involve comparing a sample with the reference.

Applicants further believe, as above, that the amount of experimentation would not be undue in light of the specification, as Applicants have provided a working example demonstrating how one of skill in the art can identify an informative gene, how to obtain an expression profile of the gene, and how to analyze the expression profiles with respect to classes of lymphoma, treatment outcome, survival and lymphoma type (see the Specification, for example, at page 13, line 25 through page 14, line 22).

In light of the above comments, Applicants maintain that one of skill in the art would clearly be enabled to practice the claimed invention without undue experimentation. A skilled artisan, by following the methods disclosed in the Specification and utilizing knowledge in the

art at the time of filing, would be enabled to make and/or use the invention as claimed. Therefore, reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-5, 8, 15-20 and 37-40 Under 35 U.S.C. §112, Second Paragraph

Claims 1-5, 8, 15-20 and 37-40 are rejected under 35 U.S.C. §112, second paragraph, for failing to point out and distinctly claim the subject matter that the Applicants regard as their invention.

Specifically, the Examiner asserts that Claims 1-5, 8, 15-20 and 37-40 are indefinite because of the recitation of the expression "the gene expression profile is correlated with a treatment outcome." The Examiner also asserts that Claims 15-20 and 39-40 are indefinite because of the recitation in Claim 15 that "the gene expression profile is correlated with a lymphoma type." Specifically, the Examiner asserts that the term, "correlated" is a non-specific relational term.

Applicants respectfully disagree. Applicants disclose and reference a variety of methods for determining whether a sample gene expression profile correlates to a reference gene expression profile (see, for example, page 11, lines 17-23). Additionally, Applicants further point out that the use of the term does not deviate from the common statistical usage; for example, as defined on the website "dictionary.com", the term means "[t]he simultaneous change in value of two numerically valued random variables: the positive correlation between cigarette smoking and the incidence of lung cancer; the negative correlation between age and normal vision."

In light of the disclosure in the Specification at, for example, page 9, lines 10-13; page 11, line 17 through page 12, line 19; and page 14, lines 10-22, Applicants believe that the use of the term, "correlated", is sufficiently described and known such that Claims 1 and 15 and claims that depend therefrom are definite. Therefore, reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-4 and 15-19 Under 35 U.S.C. §102

Claims 1-4 and 15-19 are rejected under 35 U.S.C §102 as being anticipated by Dalla-Favera and Chaganti (U.S. Patent Number 5,882,858, filed May 28, 1996, issued March 16,

1999; Reference AT). The Examiner asserts that Dalla-Favera and Chaganti teach a method of classifying a lymphoma sample according to predicted treatment outcome comprising (a) isolating a gene expression product from at least one informative gene, and (b) determining a gene expression profile of at least one informative gene, and further that the gene expression profile determined by this method correlates to treatment outcome.

Applicants have amended Claims 1 and 15 to recite "two or more informative genes." As such, Dalla-Favera and Chaganti do not teach the method of Claims 1 and 15. Applicants further note that Claims 2-4 and 16-19 depend from Claims 1 and 15, respectively, and, since the limitations of the parent claims are not anticipated by Dalla-Favera and Chaganti, the dependent claims cannot be anticipated by Dalla-Favera and Chaganti.

Rejection of Claims 5, 20 and 37-40 Under 35 U.S.C. §103(a)

Claims 5, 20 and 37-40 are rejected under 35 U.S.C. §103(a) as being unpatentable over Dalla-Favera in view of Perou *et al.* (1999, *Proc. Natl. Acad. Sci. USA*, 96:9212-9217). In addition to the teachings of Dalla-Favera and Chaganti (above), the Examiner asserts that the teachings of Perou *et al.* render performing the invention of Claims 5, 20 and 37-40 obvious, as Perou *et al.* teach the demonstrated ability of a microarray to detect changes in a broad variety of genes in a single experiment.

As above, Applicants note that Claims 1 and 15 have been amended to recite "two or more informative genes." Applicants further note that Claims 5, 20 and 37-40 depend from either Claim 1 or 15. Therefore, the teachings of Dalla-Favera and Chaganti do not disclose the subject matter of Claims 1 and 15 with respect to "two or more informative genes." Applicants further note that Perou *et al.* do not teach a method of classifying a sample according to lymphoma type comprising isolating a gene expression product from two or more informative genes from one or more cells in said sample. Therefore the teachings of Dalla-Favera and Chaganti in light of Perou *et al.* do not render Claims 5, 20 and 37-40 obvious. Therefore, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Amended) A method of classifying a lymphoma sample according to predicted treatment outcome comprising the steps of:

   a) isolating a gene expression product from two or more [at least one] informative genes [gene] from one or more cells in said sample; and

   b) determining a gene expression profile of two or more of the [at least one] informative genes [gene],

   wherein the gene expression profile is correlated with a treatment outcome, thereby classifying the sample with respect to treatment outcome.

4. (Amended) A method according to Claim 3, wherein the gene expression profile is determined using hybridization probes specific to two or more of the [at least one] informative genes [gene].

15. (Amended) A method of classifying a sample according to lymphoma type comprising the steps of:

   a) isolating a gene expression product from two or more [at least one] informative genes [gene] from one or more cells in said sample; and

   b) determining a gene expression profile of two or more of the [at least one] informative genes [gene],

   wherein the gene expression profile is correlated with a lymphoma type, thereby classifying the sample with respect to lymphoma type.

19. (Amended) A method according to Claim 18, wherein the gene expression profile is determined using hybridization probes specific to two or [one ore] more of the informative genes.

37. (Amended) The method of Claim 1, wherein a gene expression product is isolated from at least five informative genes from one or more cells in said sample and wherein a gene expression profile of said at least five informative genes is determined.

38. (Amended) The method of Claim 1, wherein a gene expression product is isolated from at least ten informative genes from one or more cells in said sample and wherein a gene expression profile of said at least ten informative genes is determined.

39. (Amended) The method of Claim 15, wherein a gene expression product is isolated from at least five informative genes from one or more cells in said sample and wherein a gene expression profile of said at least five informative genes is determined.

40. (Amended) The method of Claim 15, wherein a gene expression product is isolated from at least ten informative genes from one or more cells in said sample and wherein a gene expression profile of said at least ten informative genes is determined.